National Stroke Project - Atrial Fibrillation
Annotated Clinical Bibliography
Revised October 2000

Clinical Trials Related to Atrial Fibrillation: Warfarin Use

Aronow WS et al. Effect of warfarin versus aspirin on the incidence of new thromboembolic stroke in older persons with chronic atrial fibrillation and abnormal and normal left ventricular ejection fraction. *Am J Cardiol* Apr 15, 2000;85(8):1033-5.

This study reports on 36-month follow-up data from 350 older persons with chronic AF showing the effect of warfarin versus aspirin on the incidence of new thromboembolic stroke in persons with abnormal and normal left ventricular ejection fraction (LVEF). In an observational study, 117 men and 233 women (age range from 60 to 101) with chronic AF in a long-term health care facility who had their LVEF measured by echocardiogram were followed for new thromboembolic stroke for approximately 36 months. Full-time staff physicians caring for the subjects administered long-term oral aspirin 325 milligrams per day to 209 persons and oral warfarin in an adjusted dose to maintain the INR between 2.0 and 3.0 to 141 persons. The physicians were more likely to prescribe warfarin if they believed that the subjects were at high risk for developing stroke and had no contraindications to warfarin (including a history of falls). Six of 141 persons (4 percent) discontinued warfarin and 6 of 209 persons (3 percent) discontinued aspirin because of adverse effects. The data showed that, compared with aspirin, warfarin administered in a dose to maintain an INR between 2.0 and 3.0 resulted in a 40 percent reduction in thromboembolic stroke in persons with prior stroke, a 31 percent decrease in thromboembolic stroke in persons with no prior stroke, a 45 percent reduction in thromboembolic stroke in persons with abnormal LVEF, and 36 percent decrease in thromboembolic stroke in persons with normal LVEF. (These findings were statistically significant.)

Atrial Fibrillation Investigators. Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation. Analysis of pooled data from 5 randomized controlled trials. *Arch Intern Med*; Jul 11, 1994;154(13):1449-57.

Analysis of pooled data from five randomized trials. Conclusions: warfarin consistently decreased the risk of stroke in patients with atrial fibrillation (68 percent reduction) with virtually no increase in the frequency of major bleeding. Patients with atrial fibrillation younger than 65 years of age without a history of hypertension, previous stroke or transient ischemic attack, or diabetes were at very low risk of stroke even when not treated. The efficacy of aspirin was less consistent.

The Boston Area Anticoagulation Trial for Atrial Fibrillation Investigators. The effect of low-dose warfarin on the risk of stroke in patients with nonrheumatic atrial fibrillation. *N Engl J Med*; Nov 29, 1990;323(22):1505-11.

Unblinded, randomized, controlled trial of long-term, low-dose warfarin therapy in patients with nonrheumatic atrial fibrillation involving 420 patients followed for an average of 2.2 years. The control group was not given warfarin but could choose to take aspirin. Conclusions: long-term low-dose warfarin therapy is highly effective in preventing stroke in patients with non-rheumatic atrial fibrillation, and can be quite safe with careful monitoring.

Connolly SJ, Laupacis A, Gent M, et al. Canadian Atrial Fibrillation Anticoagulation (CAFA) Study. *J Am Coll Cardiol*; Aug 1991; 18(2):349-55.

Double-blind, placebo-controlled trial to assess the potential of warfarin to reduce systemic thromboembolism and its inherent risk of hemorrhage. One hundred and eighty-seven patients were allocated to warfarin and 191 to placebo. As a result of the publication of two other "positive" studies of similar design and objective, this study was stopped early before completion of its planned recruitment of patients. Conclusions: The estimate of benefit of anticoagulant therapy in atrial fibrillation (relative risk reduction of 37 percent) was consistent with estimates from previous reports and supported the use of warfarin in patients with nonrheumatic valvular atrial fibrillation.

EAFT (European Atrial Fibrillation Study Group). Secondary prevention in non-rheumatic atrial fibrillation after minor transient ischemic attack or minor stroke. *Lancet*; Nov 20, 1993; 342(8882): 1255-62.

Physicians in 108 centers and 13 countries collaborated in this randomized trial using open anticoagulation or double-blind treatment with either aspirin or placebo. There were 1007 patients with nonrheumatic atrial fibrillation and recent transient ischemic attack or minor ischemic stroke followed for 2-3 years. Conclusions: anticoagulation is effective in reducing the risk of recurrent vascular events in patients with nonrheumatic atrial fibrillation (90 vascular events are prevented if 1000 patients are treated with anticoagulation for one year).

Ezekowitz MD, Bridgers SL, James KE et al. Warfarin in the prevention of stroke associated with nonrheumatic atrial fibrillation. Veterans Affairs Stroke Prevention in Nonrheumatic Atrial Fibrillation Investigators. *N Engl J Med*; Nov 12, 1992; 327(20):1406-12.

Randomized, double-blind, placebo-controlled study to evaluate low-intensity warfarin treatment in 571 patients with nonrheumatic atrial fibrillation. The reduction in risk with warfarin therapy was 79 percent. Conclusions: low-intensity anticoagulation with warfarin prevented cerebral infarction in patients with nonrheumatic atrial fibrillation without producing an excess risk of major hemorrhage. The benefit extended to patients over 70 years of age.

Peterson P, Boysen G, Godtfredsen J et al. Placebo-controlled randomized trial of warfarin for prevention of thromboembolic complications in chronic atrial fibrillation: the Copenhagen AFASAK study. *Lancet*; Jan 28, 1989;I(8631):175-9.

Double-blind study in which patients (1007) with chronic non-rheumatic atrial fibrillation were randomized; approximately one-third received warfarin alone, one-third received aspirin, and one-third received placebos. Each patient was followed for two years or until termination of the trial. Conclusions: the incidence of thromboembolic complication or death was significantly lower in the warfarin group than in the aspirin or placebo groups. Anticoagulation therapy with warfarin was recommended to prevent thromboembolic complications in patients with chronic, non-rheumatic atrial fibrillation.

Stroke Prevention in Atrial Fibrillation Investigators. Stroke Prevention in Atrial Fibrillation Study. Final Results. *Circulation;* Aug 1991;84(2):527-39.

Double blind, multicenter, randomized trial that compared aspirin or warfarin with placebo and involved 1,330 inpatients and outpatients followed for 1.3 years. Primary events or death were reduced by 58 percent by warfarin and 32 percent by aspirin. The risk of significant bleeding was 1.5, 1.4 and 1.6 percent per year in patients assigned to warfarin, aspirin and placebo, respectively. Conclusions: Aspirin and warfarin are both effective in reducing ischemic stroke and systemic embolism in patients with atrial fibrillation. Because warfarin-eligible patients composed a subset of all aspirin-eligible patients, the magnitude of reduction in events by warfarin versus aspirin cannot be compared. Too few events occurred in warfarin-eligible patients to directly assess the relative benefit of aspirin compared to warfarin, and the trial is continuing to address this issue. Patients with nonrheumatic atrial fibrillation who can safely take either aspirin or warfarin should receive prophylactic antithrombotic therapy to reduce the risk of stroke.

Stroke Prevention in Atrial Fibrillation Investigators. Warfarin versus aspirin for the prevention of thromboembolism in atrial fibrillation. The stroke prevention in atrial fibrillation II study. *Lancet*; Mar 19, 1994;343(8899):687-91.

Warfarin was compared with aspirin in two parallel randomized trials involving 715 patients approximately 75 years of age or less and 385 patients older than 75 years of age. This study was an extension of the SPAF-I trial (which was limited by the small number of thromboembolic events) and sought to assess the differential effects of warfarin versus aspirin according to age. Conclusions: warfarin may be more effective than aspirin for prevention of ischemic stroke in patients with atrial fibrillation, but the absolute reduction in stroke rate by warfarin is small. Younger patients without risk factors had a low rate of stroke when treated with aspirin. In older patients, the rate of stroke was substantial no matter which therapy was used.

Yamaguchi T. Optimal intensity of warfarin therapy for secondary prevention of stroke in patients with nonvalvular atrial fibrillation: a multicenter, prospective, randomized trial, Japanese Nonvalvular Atrial Fibrillation – Embolism Secondary Prevention Cooperative Study Group. *Stroke* Apr 2000;31(4):817-21.

The optimal intensity of warfarin therapy for secondary prevention of stroke in nonvalvular AF (NVAF) remains unclear. The Embolism Secondary Prevention Cooperative Study Group studied the efficacy and safety of conventional (INR 2.2-3.5) and low-intensity (INR 1.5-2.1) warfarin therapy in a prospective, randomized, multicenter trial. Patients younger than 80 years were eligible if they had definite or possible cardioembolic stroke or TIA due to NVAF at one to six months prior to entry in the study. After the patient's eligibility was confirmed, he or she was randomly assigned to receive either conventional- or low-intensity warfarin therapy. Prothrombin time (INR) and end point events (occurrence of stroke, TIA, and adverse effects) were assessed and recorded by the stroke specialists. The frequency of patients with severe bleeding in the conventional-intensity group was significantly higher than that in the low-intensity group. No difference in stroke recurrence between the two groups was observed at the time of termination. Patient

recruitment was terminated after the disclosure of an increased rate of life-threatening bleeding in the conventional-intensity group compared with the low-intensity group was noted. It is important to note that the numbers of patients involved in this study were small (115), and the upper range of the INR was higher than the standard in the United States. The cultural and dietary differences between American and Japanese patients could also have made a significant impact on the efficacy of warfarin.

Reviews of the Clinical Trials

Akhtar W, et al. Indications for anticoagulation in atrial fibrillation. *Am Fam Phy*; Jul 1998; 58(1):130-6.

A review of the clinical trials from a primary care perspective. The authors recommend that patients with atrial fibrillation and other risk factors for stroke receive warfarin regardless of their age. In patients who are < 65 years of age and have no other risk factors for stroke, either aspirin or no therapy at all is recommended. Aspirin or warfarin therapy is recommended for patients between the ages of 65 and 75 with no other risk factors, and warfarin is recommended for use in patients > 75 years of age.

Benavente O et al. Antiplatelet therapy for preventing stroke in patients with nonvalvular atrial fibrillation and no previous history of stroke or transient ischemic attacks. *Cochrane Database Syst Rev 2000;(2):CD001925*.

The objective of this review was to determine the efficacy and safety of antiplatelet therapy for prevention of stroke in patients with chronic non-valvular AF. All randomized trials comparing antiplatelet therapies to placebo in patients with non-valvular AF and no history of transient ischemic attack (TIA) or stroke were reviewed. Among 1,680 participants without prior stroke/TIA, randomized to aspirin or placebo in two trials, aspirin was associated with nonsignificantly lower risks of ischemic stroke and the constellation of stroke, MI or vascular death. Considering all randomized participants including those with prior stroke or TIA, reductions in these events by aspirin were consistently smaller. No increase in major hemorrhage was seen, but the number of hemorrhagic events was small. Considering all randomized data, aspirin modestly reduces stroke and major vascular events in nonvalvular AF. For primary prevention among AF patients with an average stroke rate of 4.5 percent per year, about 10 strokes would be prevented yearly for every 1000 given aspirin.

Benavente O, Hart R et al. Oral anticoagulants for preventing stroke in patients with non-valvular atrial fibrillation and no previous history of stroke or transient ischemic attacks. *Cochrane Database of Systematic Reviews* 2000.

The objective of this review was to characterize the efficacy and safety of oral anticoagulation with vitamin K antagonists for the primary prevention of stroke in patient with chronic AF. All randomized controlled trials comparing the value of oral anticoagulation versus control in patients with nonvalvular chronic AF and no history of TIA or stroke were included. Of 2,313 participants without prior cerebral ischemia from five trials, about half were randomized to adjusted-dose

oral anticoagulation with an estimated mean INR ranging between 2.0-2.6 during 1.5 years/participant average follow-up. Oral anticoagulation was associated with large, highly statistically significant reductions in ischemic stroke, MI or vascular death. These benefits were not substantially offset by increased bleeding among participants in randomized clinical trials. For primary prevention in AF patients who have an average stroke rate of 4 percent per year, about 25 strokes and about 12 disabling fatal strokes would be prevented yearly for every 1,000 give oral anticoagulation.

Dalen JE. Atrial fibrillation: reducing stroke risk with low-dose anticoagulation. *Geriatrics*; May 1994; 49(5):24-6, 29-32.

A review five major clinical trials from the co-chairman of the American College of Chest Physicians atrial fibrillation consensus statement committee.

Gershlick AH. Treating the non-electrical risks of atrial fibrillation. *Eur Heart J*; May 1997; 18(Suppl C):C19-26.

A review of the randomized trials. The different risk stratification schemes and their specific relationship to recommended therapies are discussed.

Hart RG et al. Antithrombotic therapy to prevent stroke in patients with atrial fibrillation: a meta-analysis. *Ann Intern Med* 1999;131:492-501.

This meta-analysis presents all currently available trials to further characterize the comparative efficacy and safety of antithrombotic therapy for the prevention of stroke in patients with AF. Two reviewers independently extracted data from published sources on the number of patients treated, total follow-up exposure, and the occurrence of five outcomes by intention-to-treat analysis: all strokes (hemorrhagic and ischemic) all causes of mortality, and major extracranial bleeding. Meta-analysis showed that adjusted-dose warfarin reduced overall relative risk for all strokes by 36 percent compared with aspirin. The increased risk for major hemorrhage associated with antithrombotic agents does not offset this benefit. The occurrence of all strokes is reduced approximately 60 percent by adjusted-dose warfarin compared with no treatment.

Koudstaal PJ. Anticoagulants versus antiplatelet therapy for preventing stroke in patients with nonrheumatic atrial fibrillation and a history of stroke or transient ischemic attacks. *Cochrane Database Syst Rev 2000;(2):CD000187.*

The objective of this review was to compare the effect of anticoagulants with antiplatelet therapy, for secondary prevention in people with nonrheumatic AF and previous cerebral ischemia. Randomized trials comparing oral anticoagulants with aspirin in patients with non-rheumatic AF and a previous transient ischemic attack or minor ischemic stroke were reviewed. Anticoagulant therapy approximately halved the odds of serious vascular events. This equates to preventing an extra 50 vascular events per year for every 1000 patients treated. Anticoagulant therapy decreased the odds of recurrent stroke by two-thirds. This translates to preventing an extra 60 strokes for every 1000 patients treated per year. The evidence from one trial suggests that anticoagulant therapy

can benefit people with nonrheumatic atrial fibrillation and recent cerebral ischemia. Aspirin may be a useful alternative if there is a contraindication to anticoagulant therapy. The risk of adverse events appears to be higher with anticoagulant therapy than aspirin.

Koudstaal PJ. Antiplatelet therapy for preventing stroke in patients with nonrheumatic atrial fibrillation and a history of stroke or transient ischemic attacks. *Cochrane Database Syst Rev* 2000;(2):CD000186.

The objective of this review was to assess the effect of antiplatelet therapy for secondary prevention in people with nonrheumatic AF and a previous transient ischemic attack or ischemic stroke. All randomized trials comparing an antiplatelet agent with placebo or open control in people with nonrheumatic AF and a previous transient ischemic attack or minor ischemic stroke were reviewed. This review includes 404 aspirin-treated patients and 378 placebo patients in total. The mean follow-up was 2.3 years. No difference was shown between aspirin and placebo in the annual rate of all vascular events, including vascular death, recurrent stroke (ischemic or hemorrhagic), myocardial infarction, and systemic embolism. Aspirin may prevent 40 vascular events per 1000 patients treated for one year. There was a non-significant reduction in the risk of recurrent stroke from 12 percent to 10 percent per year. The incidence of major bleeding events requiring hospitalization, blood transfusions or surgical treatment was low. Aspirin may reduce the risk of vascular events in people with nonrheumatic atrial fibrillation, but the effect shown in the single trial was not statistically significant.

Morley J, et al. Atrial fibrillation, anticoagulation, and stroke. *Am J Cardiol*; Jan 25, 1996; 77(3): 38A-44A.

A review of the six major clinical trials with a meta-analysis revealing a 64 percent reduction of risk for stroke in patients treated with warfarin, as compared with placebo. The authors conclude that the value of warfarin therapy in patients > 75 years old is less clear because of a high risk of hemorrhagic complications.

Nademannee K, et al. Long-term antithrombotic treatment for atrial fibrillation. *Am J Cardiol*; Oct 16, 1998: 82(8A):37N-42N.

A review of the first five published clinical trials which recommends adherence to the guidelines from the American College of Chest Physicians (Laupacis A et al. Antithrombotic therapy in atrial fibrillation. *Chest*; Nov 1998;114(5Suppl):579S-589S).

Nelson KM, et al. Preventing stroke in patients with nonrheumatic atrial fibrillation. *Am J Hosp Pharm*; May 1, 1994; 51(9):1175-83.

A review of the six randomized clinical trials from a clinical pharmacy perspective.

Wolf PA, et al. Preventing stroke in atrial fibrillation. *Am Fam Phy*; Dec 1997; 56(9):2242-50.

A review article written for a primary care physician audience in collaboration with the American Heart Association. The authors conclude that warfarin is efficacious in stroke prevention for patients with atrial

fibrillation and that this anticoagulation benefit is achieved with an acceptably low risk of serious hemorrhage.

Additional Articles and Studies Evaluating Other Antiplatelet Agents or Procedures

Berge E et al. Low molecular-weight heparin versus aspirin inpatients with acute ischaemic stroke and atrial fibrillation: a double-blind randomised study. HAEST Study Group. Heparin in Acute Embolic Stroke Trial. *Lancet* Apr 8, 2000;355(9211):1205-10.

Heparin in Acute Embolic Stroke Trial (HAEST) was a multicenter, randomized, double-blind trial on the effect of low-molecular-weight (LMW) heparin or aspirin for the treatment of 449 patients with acute ischemic stroke and atrial fibrillation. The primary aim was to test whether treatment with LMW heparin, started within 30 hours of stroke onset, is superior to aspirin for the prevention of recurrent stroke during the first 14 days. The frequency of recurrent ischemic stroke during the first 14 days was 19/244 (8.5 percent) in LMW heparin-allocated patients versus 17/225 (7.5 percent) in aspirin-allocated patients. There were no significant differences in functional outcome or death at 14 days, or three months. The present data do not provide any evidence that LMW heparin is superior to aspirin for the treatment of acute ischemic stroke in patients with AF.

Chandramouli BV, et al. Atrial fibrillation: preventing thromboembolism and choosing nondrug therapies. *Geriatrics*; Jul 1998; 53(7):53-60.

A discussion paper regarding the use of cardioversion and pacemakers when a trial of antiarrhythmic drug therapy has failed or is contraindicated.

Disch DL, Greenberg ML, Holzberger PT et al. Managing chronic atrial fibrillation: A Markov decision analysis comparing warfarin, quinidine, and low-dose amiodarone. *Ann Intern Med*; Mar 15, 1994;120(6):449-57.

In this hypothetical cohort, fewer patient had disabling events with amiodarone than with quinidine, warfarin or no treatment. In terms of quality-adjusted life-years, amiodarone had the highest expected value, followed by warfarin, quinidine and no treatment. Rates for 5-year mortality were calculated: amiodarone (4.75 years), warfarin (4.72 years), quinidine (4.68 years), and no treatment (4.55 years). Cardioversion followed by low-dose amiodarone to maintain normal sinus rhythm appears to be a relatively safe and effective treatment for patients with chronic atrial fibrillation.

Middlekauff HR, Stevenson WG, Gorbein JA. Antiarrhythmic prophylaxis vs warfarin anticoagulation to prevent thromboembolic events among patients with atrial fibrillation. A decision analysis. *Arch Intern Med*; May 8, 1995;155(9):913-20.

Based on data from randomized, controlled trials of quinidine and warfarin, warfarin therapy appears to be the safest strategy for thromboembolism prevention in patients with atrial fibrillation. The role of low-dose amiodarone therapy appears promising and warrants further study in randomized controlled trials.

Morocutti C, Amabile G, Fattapposta F et al. Indobufen versus warfarin in the secondary prevention of major vascular events in nonrheumatic atrial fibrillation. SIFA investigators. *Stroke*; May 1997; 28(5):1015-21.

Randomized trial involving 916 patients with nonrheumatic atrial fibrillation and a recent cerebral ischemic episode comparing indobufen and warfarin for 12 months. At the end of follow-up, the incidence of primary outcome events was 10.6 percent in the indobufen group and 9.0 percent in the warfarin group with no statistically significant difference between treatments. The frequency of noncerebral major bleeding complications was low and all were observed in the warfarin group.

Pengo V, Zasso A, Barbero F et al. Effectiveness of fixed minidose warfarin in the prevention of thromboembolism and vascular death in nonrheumatic atrial fibrillation. *Am J Cardiol*; Aug 15, 1998;82(4):433-7.

Patients > 60 years of age with nonrheumatic atrial fibrillation were randomized in an open-labeled trial to received fixed minidose warfarin or standard adjusted-dose warfarin. Mean follow-up was 14.5 months. The rate of ischemic stroke was significantly higher in the minidose group. Major bleeding was more frequent in the standard treatment group. The significantly increased occurrence of ischemic stroke in the fixed minidose warfarin group suggests that this regimen does not protect patients with nonrheumatic atrial fibrillation.

SPAF investigators. Adjusted-dose warfarin versus low-intensity, fixed-dose warfarin plus aspirin for high-risk patients with atrial fibrillation: Stroke Prevention in Atrial Fibrillation III randomized clinical trial. *Lancet;* Sep 7, 1996;348(9028):633-8.

Randomized, unblinded trial involving 1044 patients with atrial fibrillation and at least one additional thromboembolic risk factor. Each was assigned either a combination of low-intensity, fixed-dose warfarin and aspirin or adjusted-dose warfarin. Conclusions: low-intensity, fixed-dose warfarin plus aspirin was insufficient for stroke prevention in patients with nonvalvular atrial fibrillation at high risk for thromboemolism. Adjusted-dose warfarin importantly reduces stroke for high-risk patients.

Consensus Statements and/or Clinical Guidelines

Gorelick PB et al. Prevention of first stroke: a review of guidelines and a multidisciplinary consensus statement from the National Stroke Association. *JAMA*; March 24/31, 1999; 281(12):1112-1120.

A consensus paper from the National Stroke Association offering, in a single resource, up-to-date recommendations for primary care physicians regarding prevention strategies for a first stroke. Warfarin therapy is recommended for patients with atrial fibrillation and specific risk factors for stroke (i.e., previous TIA, systemic embolus, or stroke; hypertension and left ventricular dysfunction). The authors also recommend aspirin therapy for patients < 65 years of age with atrial fibrillation who have no additional risk factors and aspirin or warfarin for patients 65 to 75 years of age with no additional risk factors.

Hart RG et al. Prevention of stroke in patients with nonvalvular atrial fibrillation. *Neurology*; Sep 1998 51(3):674-81.

Practice guidelines from the American Academy of Neurology with specific recommendations for warfarin and or aspirin therapy for patients with atrial fibrillation using three stroke risk stratification categories: 1) high risk; 2) moderate risk; and 3) low risk. High risk factors for stroke include: hypertension, diabetes, prior stroke or TIA, coronary artery disease, congestive heart failure (including left ventricular dysfunction), and/or female gender and > 75 years of age. These guidelines recommend a higher dose of warfarin to achieve an INR goal of 3.0 for patients with prior stroke or TIA and low bleeding risk.

Laupacis A et al. Antithrombotic therapy in atrial fibrillation. *Chest*; Nov 1998;114(5Suppl):579S-589S.

Practice guidelines from the American College of Chest Physicians which recommend warfarin therapy for patients with atrial fibrillation and any of the following risk factors for stroke: prior TIA, systemic embolus or stroke, poor left ventricular function, rheumatic mitral valve disease, prosthetic heart valve, hypertension and current congestive heart failure/poor systolic function. The authors also recommend aspirin therapy for patients < 65 years of age with atrial fibrillation who have no additional risk factors for stroke. These guidelines were updated from a previous set of guidelines published in 1996.

Prystowsky EN et al. Management of patients with atrial fibrillation. *Circulation*; Mar 15, 1996; 93(6):1262-77.

Practice guidelines from the American Heart Association Subcommittee on Electrocardiography and Electrophysiology recommending warfarin therapy for patients with atrial fibrillation and any of the following risk factors for stroke: history of hypertension, prior stroke or TIA, diabetes, recent heart failure, and age > 65 years. The authors also recommend aspirin therapy for patients < 65 years of age with atrial fibrillation who have no additional risk factors for stroke.

Report of the Quality Standards Subcommittee of the American Academy of Neurology. Practice parameter: stroke prevention in patients with nonvalvular atrial fibrillation. *Neurology*; Sep 1998; 51(3):671-73.

An executive summary of the American Academy of Neurology guidelines referenced above in: Hart RG et al. Prevention of stroke in patients with nonvalvular atrial fibrillation. *Neurology*; Sep 1998 51(3):674-81.

Atrial Fibrillation as a Risk Factor for Stroke

Benjamin EJ et al. Independent risk factors for atrial fibrillation in a population-based cohort. The Framingham Heart Study. *JAMA*; Mar 16, 1994;271(11):840-4.

The Framingham study helped to define the risk factors for development of atrial fibrillation. They are, in men, congestive heart failure, age, valve disease, hypertension, diabetes and myocardial infarction (in decreasing value of the odds ratio). These same factors, in the same order, exist for women except for myocardial infarction. Modification of risk factors for

cardiovascular disease may have the added benefit of diminishing the incidence of atrial fibrillation.

Fisher CM. Reducing risks of cerebral embolism. *Geriatrics;* Feb 1979;34(12):59-61.

While valvular heart disease is a recognized cause of atrial fibrillation, the majority of elderly patients with strokes associated with this arrhythmia have nonvalvular atrial fibrillation.

Pozzoli M et al. Predictors of primary atrial fibrillation and concomitant clinical and hemodynamic changes in patients with chronic congestive heart failure: a prospective study in 344 patients with baseline sinus rhythm. *J Am Coll Cardio*; Jul 1998; 32(1):197-204

A study intended to investigate the incidence, predisposing factors and significance of the onset of atrial fibrillation in patients with chronic congestive heart failure. This study showed that in patients with congestive heart failure, reversible atrial fibrillation and reduction of left atrial contribution to left ventricular filling predict the subsequent development of chronic atrial fibrillation. The onset of atrial fibrillation is associated with clinical and hemodynamic deterioration and may predispose to systemic thromboembolism and poorer prognosis.

Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation: a major contributor to stroke in the elderly. The Framingham Study. *Arch Intern Med*; Sep 1987;147(9):1561-4.

The prevalence of atrial fibrillation in stroke patients increases with age, rising from six percent in patients in the sixth decade to 31 percent in patients in the ninth decade of life. These prevalence data translate to a nearly 25 percent risk of stroke in patients 80 years old and older with atrial fibrillation.

Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke. The Framingham Study. *Stroke*; Aug 1991;22(8):983-8.

The impact of nonrheumatic atrial fibrillation, hypertension, coronary heart disease, and cardiac failure on stroke incidence was examined in 5,070 participants in the Framingham Study, after 34 years of follow-up. The incidence of atrial fibrillation increases with age, doubling with each successive decade above 55 years of age. Compared with subjects free of the condition, there was a near fivefold excess of stroke incidence with atrial fibrillation. The data suggest that the elderly are particularly vulnerable to stroke when atrial fibrillation is present, a powerful independent effect that is in accord with findings of recent randomized clinical trials in which > 50 percent of stroke events were prevented with warfarin anticoagulation.

Warfarin Use In Clinical Practice

Albers GW, Yim JM, Belew KM et al. Status of antithrombotic therapy for patients with atrial fibrillation in university hospitals. *Arch Intern Med;* Nov 11, 1996;156(20):2311-6.

A study to assess the use of antithrombotic therapy in patients with atrial fibrillation at six university hospitals (part of a member-driven alliance of 70 academic health centers across the United States). Records were reviewed from consecutive hospital admissions of 309 patients with atrial fibrillation. Out of a cohort of 134 patients with atrial fibrillation and no contraindications to warfarin, 44 percent were discharged on the drug.

Albers GW, Bittar N, Young L et al. Clinical characteristics and management of acute stroke in patients with atrial fibrillation admitted to US university hospitals. *Neurology;* Jun 1997; 48(6):1598-604.

This same group of university hospitals (see above) studied 171 consecutive patients with atrial fibrillation admitted for stroke. Data collected included the use of antithrombotic therapy, brain and cardiac imaging, bleeding complications, stroke risk factors, and contraindications to anticoagulation. Even in this setting of tertiary prevention with patients at high risk for subsequent stroke, only 47 percent of the survivors were discharged on warfarin. Also noted was inadequate monitoring of anticoagulation prior to admission (only half of the patients with stroke risk factors and no contraindications were receiving antithrombotic therapy on admission).

Antani MR, Beyth RJ, Covinsky KE. Failure to prescribe warfarin to patients with nonrheumatic atrial fibrillation. *J Gen Intern Med;* Dec 1996;11(12):713-20.

In a study based of 189 consecutive patients with nonrheumatic atrial fibrillation at two teaching hospitals and five community hospitals, only 37 percent of eligible patients received warfarin. Increasing risk factors for stroke, including age older than 75 years, were associated with decreased use of warfarin.

Blackshear JL, et al. Management of atrial fibrillation in adults: prevention of thromboembolism and symptomatic treatment. *Mayo Clin Proc*; Feb 1996; 71(2):150-60.

A discussion paper of the different stroke prevention and antiarrhythmic therapies from the Mayo Clinic

Brass LM, Krumholz HM, Scinto JM, Radford M. Warfarin use among patients with atrial fibrillation. *Stroke*; Dec 1997;28(12):2382-9.

The Connecticut PRO examined a state-wide cohort of patients hospitalized with atrial fibrillation. They identified 488 patients hospitalized in the first half of 1994, of which 184 patients (38 percent) had relative or absolute contraindications to warfarin use. Among the remaining patients, only 117 (38 percent) received warfarin. Two-thirds of the untreated patients were also not treated with aspirin.

Brass LM, Krumholz HM, Scinto JM, Radford M. Warfarin use following ischemic stroke among Medicare patients with atrial fibrillation. *Arch Intern Med;* Oct 26, 1998;158(19):2093-100.

In a study related to the study above, the Connecticut PRO determined that only 53 percent of 278 patients discharged alive with atrial fibrillation and a primary diagnosis of stroke received warfarin. Among ideal candidates, high risk for stroke and low risk for bleeding, only 62 percent received warfarin.

Brodsky et al. Regional attitudes of generalists, specialists and subspecialists about management of atrial fibrillation. *Arch Intern Med*; Dec 9-23 1996; 156:2553-62.

A survey was sent to 4500 physicians in 1996 to determine the attitudes of generalists, specialists and subspecialists regarding the management of atrial fibrillation. Physicians returning the survey (904 or 20 percent) were found to agree on most issues of atrial fibrillation management. One exception was the use of antiarrhythmic drugs.

Bungard TJ et al. Why do patients with atrial fibrillation not receive warfarin. *Arch Intern Med* Jan 10, 2000;160(1):41-6.

Available data show that only 15 percent to 44 percent of patients with AF and no contraindications, are prescribed warfarin. This literature review has identified patient-, physician-, and health care system-related barriers to warfarin prescription. Patient-related barriers include age, perceived embolic risk and perceived risk for hemorrhage. The physician's perception of the benefit versus the risk of therapy is the only consistent finding influencing the implementation of warfarin therapy. This perception, in part, is likely derived from the physician's previous experience with the use of warfarin. One survey reported that 79 percent of physicians cited a lack of patient reliability as a contraindication to therapy, and greater than 90 percent of the same group did not prescribe warfarin to patients with a history of chronic alcoholism. Of those patients admitted to the hospital with a stroke while receiving warfarin therapy, most have subtherapeutic international normalized ratios. Further work is needed to understand the discrepancy between the randomized controlled trial evidence and clinical practice patterns.

Flaker GC et al. Underutilization of antithrombotic therapy in elderly rural patients with atrial fibrillation. *Am Heart J*; Feb 1999; 137(2):307-12.

In a peer-review audit of antithrombotic use in Missouri, rural patients were given antithrombotic therapy less often than urban patients despite a similar high-risk profile and fewer relative contraindications. One reason for this discrepancy was the fact that primary care physicians prescribed antithrombotic therapy less often than cardiologists leading to underutilization in rural areas.

Gage BF et al. Adverse outcomes and predictors of underuse of antithrombotic therapy in Medicare beneficiaries with chronic atrial fibrillation. *Stroke* April 2000;31:822-827.

This study had three goals: 1) documentation of the use of antithrombotic therapy at the time of hospital discharge in Missouri Medicare beneficiaries who had chronic NVAF; 2) determination of factors associated with its underuse; and 3) determination of the association between prescription of antithrombotic therapy at discharge and adverse outcomes in clinical practice. To accomplish these goals, the Missouri Patient Care Review Foundation (MPCRF) abstracted the hospital charts of a random sample of Medicare beneficiaries with chronic AF and then linked these abstractions with national Medicare administrative databases to determine the rate of death and other adverse outcomes. Of the 1147 cases with a Medicare claim that included a diagnosis of AF, 203 cases were excluded because the AF was new onset, intermittent, or associated with valvular disease. An additional 347 cases were excluded because no EKG or rhythm strip was recorded during the index hospitalization or because that recording did not demonstrate AF. Of the remaining 597 cases with chronic NVAF documented, the median age was 80 years. Overall, 34 percent of patients were prescribed warfarin, 21 percent were prescribed aspirin and 45 percent were not prescribed any antithrombotic therapy. Advanced age, female gender and rural residency predicted underuse of antithrombotic therapy. After controlling for these factors, as

well as stroke risk factors and contraindications to anticoagulation, the prescription of warfarin was associated with a 24 percent relative risk reduction in adverse outcomes (death from any cause and hospitalization for an ischemic event). Prescription of aspirin was associated with a nonsignificant 5 percent relative risk reduction in these events.

Golden WE, et al. Arkansas Foundation for Medical Care report: preventing stroke in atrial fibrillation. *J Ark Med Soc*; Feb 1994; 90(9):439-40.

A report from the Arkansas Foundation for Medical Care on the results of one of their atrial fibrillation projects. In their sample, statewide use of warfarin for primary prophylaxis in patients under 80 years of age was 21 percent and use of either warfarin or aspirin was 42 percent. Smaller hospitals and those not located in Central Arkansas used warfarin less frequently than larger institutions for prophylaxis of stroke. Likewise, these hospitals were less likely to give any stroke prophylaxis to patients with this condition.

Gottlieb LK, et al. Anticoagulation in atrial fibrillation: does efficacy in clinical trials translate into effectiveness in practice? *Arch Intern Med*; Sep 12, 1994; 154(17):1945-53.

A study from the Harvard Community Health Plan to determine whether recommendations from clinical trials had been implemented into routine practice. The study also attempted to determine if the low complication rates achieved in clinical trials were matched in community practice.

Gurwitz JH, Monette J, Rochon PA et al. Atrial fibrillation and stroke prevention with warfarin in the long-term care setting. *Arch Intern Med;* May 12, 1997; 157(9):978-84.

In another study in long-term care facilities, 32 percent of 413 patients with atrial fibrillation were treated with warfarin. Many of these patients had contraindications to warfarin use. Also, patients were maintained within the appropriate therapeutic range only 60 percent of the time.

Ibrahim SA et al. Underutilization of oral anticoagulant therapy for stroke prevention in elderly patients with heart failure. *Am Heart J* 2000;140(2):219-20.

Data from the Cleveland Health Quality Choice database were used to identify 2,093 Medicare-insured patients ≥ 65 years of age with AF. Only 414 (20 percent) of these patients with AF received oral anticoagulant therapy. Older age and history of gastrointestinal bleeding were negatively and history of stroke or TIA were positively associated with receiving oral anticoagulant therapy. Patients with these characteristics as well as patients with a do-not-resuscitate order were excluded. Even with these exclusions, the oral anticoagulant therapy utilization rate did not change significantly (21 percent). It is possible that high frequency of comorbidity and other potential contraindications may account for lower rates of anticoagulant therapy. It is precisely this high-risk patient group that has been shown to achieve the most benefit from warfarin therapy. Paradoxically, it is also in this high-risk, older patient group that physicians most fear the possibility of major complications from anticoagulant therapy.

Kalra et al. Prospective cohort study to determine if trial efficacy of anticoagulation for stroke prevention in atrial fibrillation translates into clinical effectiveness. *BMJ* May 6, 2000;320:1236-9.

The purpose of this two-year prospective cohort study of a district general hospital was to determine whether trial efficacy of prophylaxis with warfarin for patients with AF at high risk of stroke translates into effectiveness in clinical practice. Patient characteristics, comorbidity, anticoagulation control, stroke rate and hemorrhagic complications were compared with pooled data from five randomized controlled trials. Of the 167 patients with AF and at high risk for stroke who received long-term anticoagulation, the INR was in the target range 61 percent of the time, below INR target ranges 26 percent of the time and above 13 percent of the time. Patients were older, included more women and spent significantly less time in the target range than patients in the randomized trials. Despite these differences, the incidence of stroke (major and minor bleeding complications) in the study group was comparable to that of patients receiving warfarin in pooled studies.

Lackner TE, Battis GN. Use of warfarin for nonvalvular atrial fibrillation in nursing home patients. *Arch Fam Med;* Dec 1995;4(12):1017-26.

In a study based in five long-term care facilities, the records of 85 patients with valvular or nonvalvular atrial fibrillation were reviewed. Only 20 percent of patients without contraindications received warfarin, and less than half of these had PT ratios or INRs in the recommended range.

Lawson F, McAlister F, Ackman M et al. The utilization of antithrombotic prophylaxis in a geriatric rehabilitation hospital. *J Am Geriatr Soc;* Jun 1996;44(6):708-11.

In the setting of a geriatric rehabilitation hospital, over half the patients were found to have contraindications to warfarin therapy. Of the 35 patients without contraindications, 25 (71 percent) were on warfarin. In addition, of the 43 patients with contraindications to warfarin but no contraindications to aspirin, only 28 were prescribed antithrombotic therapy.

Lip GY, Golding DJ, Nazir M et al. A survey of atrial fibrillation in general practice: the West Birmingham Atrial Fibrillation Project. *Br J Gen Pract*; May 1, 1997;47(418):285-9.

This British study investigated the prevalence, clinical features and management of patients with atrial fibrillation in a general practice setting. Chart abstraction of 111 patients in two general practices. Warfarin was prescribed to only 40 patients (36 percent) and of those not prescribed warfarin, only 12 patients (17 percent) had contraindications to warfarin therapy.

Mendelson G, Aronow WS. Underutilization of warfarin in older persons with chronic nonvalvular atrial fibrillation at high risk for developing stroke. *J Am Geriatr Soc*; Nov 1998; 46(11):1423-4.

In an academic geriatric practice, 49 percent of 127 high-risk (previous thromboembolism, congestive heart failure, abnormal left ventricular systolic function, systolic blood pressure > 160 mm Hg, or female > 75 years of age) patients with no contraindications to warfarin were treated with warfarin as recommended by the clinical trials.

Munschauer FE, Priore RL, Hens M et al. Thromboembolism prophylaxis in chronic atrial fibrillation. Practice patterns in community and tertiary-care hospitals. *Stroke;* Jan 1997;28(1):72-6.

In a study of 651 patients with chronic atrial fibrillation of all causes, only 34 percent (219) were treated with warfarin. Another 22 percent (146) were treated with antiplatelet agents and 2 percent (13) received both. Multivariate logistic regression indicated that the decision to treat was associated only with the presence of prosthetic valve, history of prior stroke, mitral disease, and absence of recent gastrointestinal bleed. This analysis also showed a bias against treatment with either warfarin or antiplatelet agents with older patients and patients discharged from community hospitals.

Samsa GP et al. Quality of anticoagulation management among patients with atrial fibrillation: results of a review of medical records from two communities. *Arch Intern Med* April 10, 2000;160(7):967-973.

Recognizing that the care of most patients at risk for stroke is provided by internists and primary care physicians, the purpose of this report was to examine comprehensively the quality of anticoagulation management by primary care physicians for ambulatory patients with AF. For patients receiving warfarin, two barriers identified include: 1) laboratory test results may not be available until after the patient has left the clinic (thus complicating the process of dosage adjustment; and 2) inadequate record-keeping systems can lead to dosage changes being communicated to the patient late or not at all and to delays in rescheduling missed appointments.

Stafford RS, Singer DE. National patterns of warfarin use in atrial fibrillation. *Arch Intern Med*; Dec 9-23, 1996;156(22):2537-41.

An analysis of 1,062 visits by patients with atrial fibrillation to randomly selected office-based physicians included in the National Ambulatory Care Surveys in 1980, 1981, 1985, and 1989 through 1993. Warfarin and aspirin use in these patients was extrapolated to national patterns and logistic regression was used to determine independent predictors. The authors found that anticoagulant use for atrial fibrillation increased dramatically from 1989 to 1993, in line with published clinical trials. However, the 1992 and 1993 rate of 32 percent was found to be suboptimal given the benefits.

The Clinical Quality Improvement Investigators. Thromboembolic prophylaxis in 3575 hospitalized patients with atrial fibrillation. *Can J Cardiol*; May 1998;14(5): 695-702.

A large Canadian study examined 3,575 patients hospitalized with atrial fibrillation. Among 2,199 patients with nonvalvular atrial fibrillation and no contraindications to anticoagulants, no more than 32 percent were treated with warfarin, and 37 percent received neither aspirin nor warfarin. Elderly and female patients were less likely to be treated.

Wheeldon NM, Tayler DI, Anagnostou E et al. Screening for atrial fibrillation in primary care. *Heart;* Jan 1998;79(1):50-5.

In a primary care practice where elderly patients were screened by electrocardiography, 65 or 5.4 percent of patients had atrial fibrillation. Only 21.4 percent of these were on warfarin, while it was determined that an additional 20 percent were eligible for anticoagulation.

White RH et al. Oral anticoagulation in patients with atrial fibrillation: adherence with guidelines in an elderly cohort. *Am J Med*; Feb 1999; 106(2):165-71.

This prospective observational study, involving four communities in the United States, studied adherence to guidelines in the care of a cohort 172 of persons age 70 years or older with a diagnosis of atrial fibrillation. Subjects were identified by atrial fibrillation on EKG at one or more yearly exams from 1993 to 1995 and were then asked to self-report their use of warfarin in 1995. Warfarin was used by 37 percent (63) of the participants who had no preexisting indication for its use. Of the 109 participants not using warfarin, 84 percent (92) had at least one clinical risk factor (aside from age) associated with stroke in patients with atrial fibrillation.

Whittle J, Wickenheiser L, Venditti LN. Is warfarin underused in the treatment of elderly persons with atrial fibrillation? *Arch Intern Med*; Feb 24, 1997;157(4):441-5.

In a study of Medicare beneficiaries at five small Pennsylvania hospitals, 44 percent of 176 eligible patients received warfarin. After implicit review of these cases by an internist and exclusion of additional patients, only 64 percent of the remaining patients had received warfarin. There was also wide variation in the use of warfarin among the five hospitals.

Changing Clinical Practices

Gaughan GL et al. Improving management of atrial fibrillation and anticoagulation in a community hospital. *Jt Comm J Qual Improv* Jan 2000;26(1):18-28.

An opportunity for improvement was identified by a community hospital regarding warfarin therapy for patients with atrial fibrillation. Only 45 percent of eligible patients were prescribed warfarin on discharge. In addition, an analysis of admission INRs indicated only a minority was safely anticoagulated. An anticoagulation clinic was established in the fall of 1997 and, in early 1998, monitoring of patients with atrial fibrillation began. Remeasurement showed that the proportion of patients receiving warfarin increased from 46 percent in February through May 1998 to 63 percent in April through June 1999. The proportion of INRs in the desired ranged increased from 49 percent to 54 percent.

Physician Attitudes Related to Warfarin Therapy

Beyth RJ, Antani MR, Covinsky KE et al. Why isn't warfarin prescribed to patients with nonrheumatic atrial fibrillation? *J Gen Intern Med;* Dec 1996;11(12):721-8.

In an American study from two university and five community hospitals, the 80 surveyed physicians recommended warfarin less often for older patients, for those with bleeding risks, and for those patients who had not experienced stroke. The physicians also reported that they prescribed warfarin for less

than half their patients for whom warfarin was thought appropriate by an independent reviewer knowledgeable about the recommendations from recent clinical trials.

Connolly SJ. Anticoagulation for patients with atrial fibrillation and risk factors for stroke. Warfarin reduces the risk by two thirds, but doctors still aren't prescribing it enough. *BMJ* May 6, 2000;320(7244):1219-20.

The most clinically relevant advance in the management of cardiac arrhythmia in the past two decades has been that anticoagulant treatment substantially reduces the risk of stroke in patients with AF. Randomized trials evaluating aspirin, low fixed dose warfarin, and their combination clearly show the superiority of warfarin, and as a result, expert panels have recommended that all patients with AF should be considered for treatment with anticoagulants. However, most patients with AF are still not prescribed warfarin by their doctors. One issue could be concern whether the beneficial effects of warfarin seen in the randomized trials will also occur in clinical practice. It is currently unknown why doctors and patients fail to implement the findings from anticoagulation trials. A better understanding of what factors actually influence patients' and doctors' behavior in this area is needed, in order to implement effective strategies.

Kellen JC, Russell ML. Physician specialty is associated with differences in warfarin use for atrial fibrillation. *Can J Cardiol*; Mar 1998;14(3):365-8.

In a survey from Alberta, Canada, 92 percent of internists and cardiologists would prescribe warfarin for elderly patients with atrial fibrillation and stroke risk compared to 76 percent of general practitioners. Specialists were more likely than GPs to prescribe warfarin for elderly patients. Physicians' intentions to prescribe warfarin for elderly patients with atrial fibrillation varied by specialty.

King D, Davies KN, Slee A, Silas JH. Atrial fibrillation in the elderly: physician attitudes to anticoagulation. *Br J Clin Pract*; May-Jun 1995;49(3):123-5.

In a British study, warfarin use for atrial fibrillation associated with dilated cardiomyopathy would have been prescribed by 52 percent of geriatricians and 86 percent of cardiologists. The figures for lone atrial fibrillation were 10 percent of geriatricians and 26 percent of cardiologists. Nearly 90 percent of both groups would prescribe warfarin for atrial fibrillation in association with mitral stenosis.

Man-Son-Hing M, Nichol G, Lau A, Laupacis A. Choosing antithrombotic therapy for elderly patients with atrial fibrillation who are at risk for falls. *Arch Intern Med*; Apr 12, 1999; 159(7):677-85.

This Canadian study explored the issue of physician reluctance to prescribe warfarin to elderly patients at risk for falls through the use of a decision analytic model. The authors concluded that, while there are many clinical factors associated with the choice of optimal antithrombotic therapy for elderly patients with atrial fibrillation, the patient's propensity for falling was not an important factor.

Mead GE, Murray H, McCollum CN, O'Neill PA. How do general practitioners manage patients at risk from stroke? *Br J Clin Pract*; Dec 1996;50(8):426-30.

A British study used a mailed survey to assess how 294 general practitioners (GPs) manage patients at risk for stroke. For patients in atrial fibrillation, most GPs (77 percent) thought that warfarin reduced stroke rates, but only 20 percent of would consider prescribing warfarin for patients with atrial fibrillation who had a recent TIA or minor stroke.

Monette J, Gurwitz JH, Rochon PA, Avorn J. Physician attitudes concerning warfarin for stroke prevention in atrial fibrillation: results of a survey of long-term care practitioners. *J Am Geriatr Soc*; Sep 1997;45(9):1060-5.

A survey of physicians caring for nursing home patients in 30 facilities in New England, Quebec and Ontario showed only 47 percent felt that the benefits of warfarin greatly outweighed the risks in these patients with atrial fibrillation. The most frequently cited contraindications to warfarin therapy were: excessive risk for falls (71 percent), history of other non-central nervous system bleeding (36 percent), and history of cerebrovascular hemorrhage (25 percent).

Patient Attitudes Related to Warfarin Therapy

Gage BF, Cardinelli AB, Albers GW, Owens DK. Cost-effectiveness of warfarin and aspirin for prophylaxis of stroke in patients with nonvalvular atrial fibrillation. *JAMA*; Dec 20, 1995; 274(23):1839-45.

Prescribing warfarin for a 65 year-old with one additional risk factor for stroke costs $8,000 per quality-of-life-year (QALY) saved. This rises to $110,000 if the patient is 75 years old or older. If the patient is 65 years old with no risk factors, the cost is $370,000. Aspirin is preferable to no therapy in terms of quality-adjusted survival and cost in all patients, with or without risk factors.

Gage BF, Cardinalli AB, Owens DK. The effect of stroke and stroke prophylaxis with aspirin or warfarin on quality of life. *Arch Intern Med*; Sep 6, 1996;156(16):1829-36.

Patients' utilities for stroke prophylaxis and anticipated stroke vary substantially. This variation was so great that the authors concluded that patients' preferences must be taken into account when choosing therapy for stroke prophylaxis. In older patients or patients with no risk factors for stroke, there was a tendency for aspirin to be the preferred therapy rather than warfarin because of the low utility some patients placed on the use of warfarin.

Man-Son-Ling M, Laupacis A, O'Conner A et al. Warfarin for atrial fibrillation. The patient's perspective. *Arch Intern Med*; Sep 9, 1996;156(16):1841-8.

The objective of this Canadian study was to determine the minimally clinically important difference (MCID) of warfarin therapy for the treatment of nonvalvular atrial fibrillation. The MCID is further defined as the smallest difference that patients perceive as beneficial related to the reduction of stroke risk by taking warfarin. Sixty-four patients with nonvalvular atrial fibrillation who had been initiated on warfarin therapy at least 3 months prior to the study were interviewed and given extensive education. Their MCIDs were much smaller than those that have been

implied by some experts and clinicians. Patients indicated a preference for warfarin therapy if it reduced their risk for stroke by 20 percent in the following two years.

Complications Related to Warfarin Therapy

Ackermann RJ. Anticoagulant therapy in patients aged 80 years or more with atrial fibrillation: more caution is needed. *Arch Fam Med*; Mar-Apr 1997; 6)2):105-10.

A discussion paper regarding the intricacies of warfarin therapy in very elderly patients with atrial fibrillation.

Albers GW et al. Antithrombotic and thrombolytic therapy for ischemic stroke. *Chest*; Nov 1998; 114(5Suppl):683S-698S.

This report focuses on new information available since the previous ACCP antithrombotic Consensus Conference, and emphasizes the therapeutic implications of recent studies of antithrombotic and thrombolytic agents for treatment or prevention of ischemic stroke.

Blackshear JL, Baker VS, Holland A et al. Fecal hemoglobin excretion in elderly patients with atrial fibrillation: combined aspirin and low-dose warfarin vs conventional warfarin therapy. *Arch Intern Med*; Mar 26, 1996;156(60:658-60.

Investigators at the Mayo Clinic looked more specifically at the potential for gastrointestinal blood loss in patients from the Atrial Fibrillation III Study. Up to 11 percent of atrial fibrillation patients on conventional adjusted-dose warfarin have occult gastrointestinal blood loss. Combined warfarin and aspirin therapy was associated with greater fecal hemoglobin excretion than standard warfarin therapy, suggesting the potential for increased gastrointestinal hemorrhage.

Dahl T, Abildgaard U, Sandset PM. Long-term anticoagulant therapy in cerebrovascular disease: does bleeding outweigh the benefit? *J Intern Med*; Mar 1995;237(3):323-9.

A study from a Norweigian university hospital to determine the risk of major hemorrhagic complications, stroke and other cardiovascular events, as well as mortality with long-term anticoagulant therapy. Data were collected retrospectively on 161 patients discharged with symptomatic cerebrovascular disease between 1983 and 1986. The rate of major (including fatal) hemorrhagic complications was 1.4 percent per year (for all patients, including those with nonvalvular atrial fibrillation).

Gallus AS. Towards the safer use of warfarin I: an overview. *J Qual Clin Pract*; Mar 1999; 19(1): 55-9.

Safe and effective warfarin treatment requires a case-by-case evaluation of each patient's clinical condition and risk factors for bleeding. Patient must also be educated so they can accept responsibility for managing their own condition. Warfarin therapy effectiveness and safety can be maximized by addressing (contra)indications for use, ongoing monitoring, and patient education/responsibility issues.

Hylek EM, Skatews SJ, Sheehan MA, Singer DE. An analysis of the lowest effective intensity of prophylactic anticoagulation for patients with nonrheumatic atrial fibrillation. *N Engl J Med*; Aug 22, 1996;335(8):540-6.

A case-control study involving 74 consecutive patients with atrial fibrillation admitted between 1989 and 1994. While these studies show that anticoagulation is not without risk, the consensus is that benefit of stroke prevention outweighs the risk even in the non-trial setting. Inadequate anticoagulation also increases the risk of stroke in patients with atrial fibrillation. At INRs below 2, the risk for stroke increases: stroke risk of 2.0 at INR 1.7, stroke risk of 3.3 at INR 1.5 and stroke risk of 6.0 at INR 1.3.

Sata Y, Honda Y, Kunoh H, Oizumi K. Long-term oral anticoagulation reduces bone mass in patients with previous hemispheric infarction and nonrheumatic atrial fibrillation. *Stroke*; Dec 1997;28(12):2390-4.

In a Japanese study, blood from patients with nonrheumatic atrial fibrillation and ischemic stroke treated with warfarin, patients with ischemic stroke but no warfarin, and patients in a control group was compared. In patients with nonrheumatic atrial fibrillation and stroke with hemiparesis, those treated with warfarin have lower bone mineral density that is probably related to the lower vitamin K concentrations and metabolism in treated patients.

The Stroke Prevention in Atrial Fibrillation Investigators. Bleeding during antithrombotic therapy in patients with atrial fibrillation. *Arch Intern Med*; Feb 26, 1996;156(4):409-16.

The Stroke Prevention in Atrial Fibrillation (SPAF) investigators looked more closely at the bleeding complications in their patients. The risk of major hemorrhage for patients on warfarin was 2.3 percent per year; the risk of intracranial hemorrhage was 0.9 percent per year. Both figures are considerably below the risk for stroke in untreated patients even if the stroke rate in warfarin-treated patients is added. Age, number of prescribed medications and higher INR were risks for hemorrhage. In the warfarin-treated patients, the risk of hemorrhage and intracranial hemorrhage was three-fold higher in patients older than 75 years compared to younger patients.

Cost-Effectiveness of Warfarin Therapy

Gage BF, Cardinalli AB, Owens DK. Cost-effectiveness of preference-based antithrombotic therapy for patients with nonvalvular atrial fibrillation. *Stroke*; Jun 1998;29(6):1083-91.

This study explored the incorporation of patient preferences into the selection of antithrombotic therapy using decision analysis. This preference-based strategy prescribed whichever antithrombotic therapy, warfarin or aspirin, had the greater projected quality-adjusted survival. The authors concluded that preference-flexible therapy should improve quality-adjusted survival and reduce medical expenditure in patients who have nonvalvular atrial fibrillation and not more than one additional risk factor for stroke.

Gage BF, Cardinelli AB, Albers GW, Owens DK. Cost-effectiveness of warfarin and aspirin for prophylaxis of stroke in patients with nonvalvular atrial fibrillation. *JAMA*; Dec 20, 1995; 274(23):1839-45.

This decision and cost-effectiveness analyses used probabilities for stroke, hemorrhage, and death from the published randomized controlled trial. Quality of life estimates were obtained from interviewing 74 patients with atrial fibrillation. Costs were estimated from literature review, telephone survey, and Medicare reimbursement data. The authors concluded that treatment with warfarin is cost-effective inpatients with nonvalvular atrial fibrillation with one or more additional risk factors for stroke. In 65 year old patients with nonvalvular atrial fibrillation but no other risk factors for stroke, prescribing warfarin instead of aspirin would affect quality-adjusted survival minimally but increase costs significantly.

Eckman MH, Falk RH, Pauker SG. Cost-effectiveness of therapies for patients with nonvalvular atrial fibrillation. *Arch Intern Med*; Aug 10-24, 1998; 158(15):1669-77.

This decision and cost-effectiveness analyses used a Markov state transition model to examine the cost-effectiveness of antithrombotic and antiarrhythmic treatment strategies for atrial fibrillation. The authors concluded that cardioversion of patients with nonvalvular atrial fibrillation followed by the use of aspirin alone or with amiodarone has a reasonable marginal cost-effectiveness ratio. While cardioversion followed by the use of amiodarone and warfarin results in the greatest gain in quality-adjusted life expectancy, it is expensive compared to aspirin and amiodarone. For patients bothered very little by symptoms of atrial fibrillation, cardioversion followed by either aspirin or warfarin without subsequent antiarrhythmic therapy is the treatment of choice.

Patient/Family/Caregiver Education Related to Warfarin

Chrzanowski DD. Managing atrial fibrillation to prevent its major complication: ischemic stroke. *Nurse Pract*; May 1998; 23(5):26, 32-7, 41-2.

A general article related to the management of atrial fibrillation from a nursing perspective. Includes a treatment algorithm and an example of patient education.

Fong LN. Balancing anticoagulant therapy. *Geriatric Nursing.* 1991 Jan-Feb; 12(1):15-7.

The role tight INR control in patients with atrial fibrillation receiving warfarin therapy, is especially important in the more elderly patient because consistent prothrombin times are difficult to maintain due to erratic food intake, instability of coexisting illness, multiple medications and confusing regimens.

Hylek EM, Skatews SJ, Sheehan MA, Singer DE. An analysis of the lowest effective intensity of prophylactic anticoagulation for patients with nonrheumatic atrial fibrillation. *N Engl J Med*; Aug 22, 1996;335(8):540-6.

A recent study designed to test the lowest effective level of prophylactic anticoagulation found that among patients with atrial fibrillation, INRs of 2.0 or greater are effective. Because the risk of hemorrhage rises rapidly at INRs greater than 4.0 to 5.0, the role of tight control of anticoagulant therapy to maintain the INRs between 2.0 and 3.0 is clear.

Echocardiography with Atrial Fibrillation

Grimm RA, et al. Should all patients undergo transesophageal echocardiography before electrical cardioversion of atrial fibrillation?; *J Am Coll Cardio*; Feb 1994, 23(2):533-541.

The use of transesophageal echocardiography (TEE) in the management of patients with atrial fibrillation continues to evolve. Because of the lack of clinical trials addressing this issue at the time of publication, TEE was not considered an established practice in all patients undergoing cardioversion at that time. However, it was evaluated as useful in screening patients for thrombus and it was suggested that TEE might enable earlier cardioversion by rendering prior prolonged anticoagulant therapy unnecessary in those patients with no evidence of atrial thrombi.

Cohen IS, Ezekowitz MD. Prevention of thromboembolism in patients with atrial fibrillation. *Cardio Clinics*; Nov 1996; 14(4):537-42.

A general summary article regarding stroke prevention strategies for patients with atrial fibrillation, including esophageal echocardiography prior to cardioversion. There is promise that high-risk patients may be identified by echocardiographic findings, especially important for evaluation of cardiogenic thrombotic risk in patients for whom electrical cardioversion is planned.

Thyroid Testing with Atrial Fibrillation

Martin FI, Deam DR. Hyperthyroidism in elderly hospitalized patients: clinical features and treatment outcomes. *Med J Aust*; Feb 19,1996; 164(4):200-203.

In 60 patients 70 years old and older with hyperthyroidism, and with low thyrotropin level (TSH) as one of the criteria, 60 percent (36 of 60) were in atrial fibrillation.

Tenerez A, Forberg R, Jansson R. Is a more active attitude warranted in patients with subclinical thyrotoxicosis? *J Intern Med*; Sep 1990; 228(3):229-33.

In patients with subclinical thyrotoxicosis, defined as low TSH with normal free thyroxine (T_4) level, 28 percent (11 of 40) were in atrial fibrillation, compared to ten percent (four of 40) in a euthyroid group. These patients had an average age of 65 years.

Pozzoli M et al. Predictors of primary atrial fibrillation and concomitant clinical and hemodynamic changes in patients with chronic congestive heart failure: a prospective study in 344 patients with baseline sinus rhythm. *J Am Coll Cardio*; Jul 1998; 32(1):197-204

In patients with congestive heart failure, 12 percent developed atrial fibrillation (28 of 344) and had consistently lower levels of TSH during a follow-up period of 19 months, 1.6 mU/L vs 2.2 mU/L for those who remained in sinus rhythm.

Sawin CT, Geller A, Wolf PA. Low serum thyrotropin concentrations as a risk factor for atrial fibrillation in older patients. *N Engl J Med*; 1994; 331:1249-52.

This study showed that low TSH is a risk factor for development of atrial fibrillation by following 2,007 patients 60 years old or older who were initially in sinus rhythm.. After ten years, follow-up was performed for the

cohort. Of the 2,007 patients, 192 developed atrial fibrillation. The relative risk of developing atrial fibrillation for patients with low TSH was 3.1 percent (3.8 percent if patients being treated for hyperthyroidism were excluded).

Anticoagulation Clinics

Ansell JE. Evolving models of warfarin management: Anticoagulation clinics, patient self-monitoring, and patient self-management. *Am Heart J;* 1996;132:1095-1100.

A reviewof anticoagulation clinic effectiveness. All showed lower, but not always significantly lower, rates of major hemorrhage for specialized care. Most did not report death rates.

Ansell JE. The quality of anticoagulation management. *Arch Int Med* April 10, 2000;160(7):1-5.

In the 1980s and 1990s, considerable effort was directed to identifying the appropriate indications for oral anticoagulation, the ideal intensity of therapy, and to improving the monitoring assay by reporting results as an INR. A growing body of evidence suggests that physicians, in the course of the usual care of their patients receiving warfarin, do not experience the same outcomes as those achieved in the randomized controlled trials. Alternatively, anticoagulation management by a systematic or coordinated process as provided in an anticoagulation service or clinic has been shown to achieve outcomes much closer to those experienced in randomized controlled trials.

Berrettini M. Anticoagulation clinics: the Italian experience. Hematological 1997;82:713-717.

A paper from Italy discussing the positive aspects of anticoagulation clinics and the current state of the art in Europe.

Landefeld GS, Goldman L. Major bleeding in outpatients treated with warfarin: incidence and prediction by factors known at the start of outpatient therapy. Am J Med 1989;87:144-152.

A study to determine the incidence of major bleeding in outpatients treated with warfarin and to identify predictive factors known at the start of therapy. Five independent risk factors for major bleeding (age 65 years or greater, history of stroke, history of gastrointestinal bleeding, a serious comorbid condition or atrial fibrillation) predicted major bleeding in the testing group. The cumulative incidence of major bleeding at 48 months was 2 percent in 54 low risk patients, 17 percent in 110 middle-risk patients, and 63 percent in 20 high risk patients. Whether risk of bleeding can be reduced in high risk patients without reducing the benefit of therapy remains to be determined.

Pell JP, Melver B, Stuart P et al. Comparison of anticoagulation control among patients attending general practice and a hospital anticoagulant clinic. Br J Gen Pract 1993;43:152-154.

An English study which showed no difference in complication rates and slighter better control and lower utilization by the group receiving routine medical care.

Chiquette E, Amato MG, Bussey HI. Comparison of an anticoagulation clinic with usual medical care: anticoagulation control, patient outcomes and health care costs. Arch Intern Med 1998;158:1641-1647.

A recent detailed study which reported results using International Normalized Ratios (INRs). The specialized clinic had 50 percent fewer patients above accepted INRs and had significantly lower rates of major hemorrhage and thromboembolic events as well as a trend toward lower death rates. However, all rates were higher than those from clinical trials.

Finh SD, McDonnell MB, Vermes D. et al. A computerized intervention to improve timing of outpatient follow-up: a multicenter randomized trial in patients treated with warfarin. J Gen Intern Med 1994;9:131-139.

This study described a system that recommended optimal follow-up time for anticoagulated patients. They compared physicians who received the computer-generated recommendation with those who did not. Patients of physicians who received the recommendations had longer intervals between appointments with no loss of anticoagulation control and no significant differences in complications. They concluded that the computer support had the potential of reducing utilization with no loss of quality of care

Fitzmaurice DA, Hobbs FD, Murray E et al. Evaluation of computerized decision support for oral anticoagulation management based in primary care. Br J Gen Pract 1996;46:533-535.

In an English study, patients were managed either locally by their primary care physicians who used a computerized decision support system or by specialized physicians without the computer system in a hospital-based anticoagulation clinic. Those patients in the arm with the computer system had far better therapeutic control (86 percent of INRs within the therapeutic limit vs 23 percent). Patients in the intervention arm also had fewer visits (mean recall time 36 days vs 24 days in the controls). Complications were similar in the control and intervention arm

Vadher BD, Patterson DL, Leaning M. Comparison of oral anticoagulant control by a nurse practitioner using a computer decision support system with that by clinicians. Clin Lab Haematol 1997;19:203-207.

An English study in which patients were assigned to an intervention group, a nurse practitioner supported by a computer decision system, or to a control group, conventional care by trainee physicians in an anticoagulation clinic. There was a trend toward better control of INRs in the intervention group. The conclusion was that equal or better control could be obtained by using a nurse practitioner with a computerized decision support system compared to physician-directed conventional care.

Galloway MJ, Foggin JJ, Dixon S. Introduction of computer assisted control of oral anticoagulation in general practice. J Clin Path 1995;48:1144-1146.

In an Australian study, a computer program was used to adjust dosage for patients managed locally by their general practitioners. Physicians sent the blood samples to a central laboratory, along with clinical information, and a recommended dose and revisit interval was generated by computer

and returned to the physicians. Patients managed in this fashion were entirely comparable in quality of control and rate of complications to a group managed using the same program but seen in a central anticoagulation clinic.

Background

Agency for Healthcare Research and Quality. *Evidence Report/Technology Assessment:* Number 12 Management of new onset atrial fibrillation summary. May 2000; 1-12.

AF is the most common arrhythmia physicians face in clinical practice, accounting for about one-third of hospitalizations for arrhythmia. This evidence report addresses the patient who presents to a clinician for the first time with AF, whether it is persistent or paroxysmal. In addition to treating underlying conditions, the management of AF is divided into three areas: ventricular rate control, cardioversion of AF and subsequent maintenance of sinus rhythm and prevention of thromboembolism. This report presents the results of an assessment of the evidence on key issues in the management of AF.

Al-Khatib SM et al. Observations on the transition from intermittent to permanent atrial fibrillation. *Am Heart J* Jul 2000;140(1):142-145.

This study was conducted to determine the proportion of patients with intermittent AF who progress to permanent AF and to investigate baseline clinical characteristics that might predict such a progression. This retrospective cohort study included 231 patients who were seen with intermittent AF from January 1978 through December 1997. Patients' medical records and electrocardiograms were reviewed and data were collected for all clinic visits through May 1998. The number of patients who remained free of transition from intermittent to permanent AF was 92 percent at one year and 82 percent at four years. Among five baseline characteristics (age, sex, structural heart disease, AF at presentation and use of an antiarrhythmic medicine before presentation), the two significant predictors of progression from intermittent to permanent AF were age and being in AF at presentation. Approximately 18 percent of patients who had intermittent AF were permanently in AF after four years of follow-up. Age and being in AF at presentation were the only two important clinical variables identified in predicting such progression.

Go AS et al. Implications of stroke risk criteria on the anticoagulation decision in nonvalvular atrial fibrillation: the anticoagulation and risk factors in atrial fibrillation (ATRIA) study. *Circ* Jul 4, 2000;102(1):11-3.

Clinical and electrocardiographic databases were used to identify 13,559 patients ambulatory patients with nonvalvular AF (NVAF) from July 1996 through December 1997. The proportion of patients classified as having a low enough stroke risk to receive aspirin was compared using published criteria from the Atrial Fibrillation Investigators (AFI), American College of Chest Physicians (ACCP), and the Stroke Prevention in Atrial Fibrillation (SPAF). AFI criteria classified 11 percent as having a low stroke risk, compared with 23 percent for ACCP and 29 percent for SPAF. The age threshold for assigning an increased stroke risk has a dramatic impact on whether to recommend warfarin in populations of patient with NVAF. Large,

prospective studies with many stroke events are needed to precisely determine the relationship of age to stroke risk in AF and to identify which AF subgroups are at a sufficiently low stroke risk to forego anticoagulation.

Gornick CC. Anticoagulant use in nonvalvular atrial fibrillation. Determining risk and choosing the safest course. *Postgrad Med* Aug 2000;108(2):113-6.

Previous TIA or stroke, diabetes, advanced age, impaired left ventricular function, and a history of hypertension are strong risk factors for stroke in patients with nonvalvular AF. When none of these factors is present, aspirin offers effective protection against future stroke. When any of these factors are present, warfarin adjusted to an INR of 2.0 to 3.0 offers greater protection against future stroke than aspirin alone or aspirin and fixed-dose warfarin (INR 1.2-1.5). More data are needed before newer anticoagulants can be recommended for treatment.

Hart RG et al. Stroke with intermittent atrial fibrillation: incidence and predictors during aspirin therapy. Stroke Prevention in Atrial Fibrillation Investigators. *Jour Amer Coll Cardiol* Jan 2000;35(1):183-7.

This study was performed to characterize the risk of stroke in elderly patients with recurrent intermittent AF. A longitudinal cohort study was performed comparing 460 participants with intermittent AF with 1,552 patient with sustained AF treated with aspirin in the Stroke Prevention in AF (SPAF) studies and followed for a mean of two years. Patients with intermittent AF were, on average, younger, more often women and less often had heart failure than those with sustained AF. Independent predictors of ischemic stroke were advancing age, hypertension and prior stroke in patients with intermittent AF. Those with intermittent AF had stroke rates similar to patients with sustained AF and similar stroke risk factors. High-risk patients with intermittent AF can be identified using the same clinical criteria that apply to patients with sustained AF.

Reiffel JA. Drug choices in the treatment of atrial fibrillation. *Am J Cardiol* May 25, 2000;85(10A):12D-19D.

The dominant issues to consider when selecting therapy for AF are recognition and treatment of any underlying disorder or precipitating condition, rate and rhythm control, and anticoagulation. Drug choices for rate control include beta-blockers, verapamil and diltiazem and digitalis as first-line agents, with consideration of other sympatholytics, amiodarone, or nonpharmacologic approaches in resistant cases. Anticoagulation may be accomplished with aspirin or warfarin, with the latter preferred in all older or high-risk patients. Antiarrhythmic drug selection for AF is guided by efficacy considerations, convenience, cost, discontinuation considerations and by safety considerations. Additional issues to consider are where to initiate therapy, what follow-up protocols to use, and whether to limit therapy to proprietary drugs or to allow generic formulation substitution.

Thomson R et al. Decision analysis and guidelines for anticoagulant therapy to prevent stroke in patients with atrial fibrillation. *Lancet* Mar 18, 2000;355(9208):956-62.

A Markov decision analysis was used to model decision-making with regard to warfarin treatment in patients with AF which involved a systematic literature

review supplemented by patients' estimates of the quality of life associated with different states of health, secondary analysis of stroke-registry data and estimation of service costs. For most risk combinations, warfarin treatment would have decreased health-care costs and increased quality-of-life years, although the clinical decision was sensitive to patients' preferences and to the estimate of warfarin's effectiveness. Approximately 97 percent of women with AF older than 75 years, and 69 percent aged 65-74 would have been recommended for treatment; for men, the corresponding figures would have been 75 percent and 53 percent. Decision analysis is useful in the incorporation of complex probabilistic data into informed decision-making, the identification of factors influencing such decisions and the subsequent development of evaluative guidelines.

Commentary

Singer DE. Antithrombotic therapy to prevent stroke in patients with atrial fibrillation. *Ann Intern Med* May 16, 2000;132(10):841-2.

In a letter to the editor, Dr D.E. Singer (Massachusetts General Hospital) noted two methodologic caveats regarding the meta-analysis of antithrombotic therapy to prevent stroke in patients with atrial fibrillation. First, the SPAF I, AFASAK, and EAFT trials are described as comparing anticoagulants to "placebo." The placebo in these trials was an aspirin placebo, not a warfarin placebo. Therefore, the potential benefit from placebo (reduced bias because of blinding) did not apply. Second, although many problems in the data supporting aspirin's effect in atrial fibrillation were highlighted, the heterogeneity in the SPAF I trials of aspirin was not directly addressed. Dr. R.G. Hart (University of Texas) responded that the heading in Table 2 of the meta-analysis was inadvertently changed from "Control group" to "Placebo group." To date, all six randomized trials (five of them double-blind) have shown trends toward reduction in stroke with aspirin use in patients with atrial fibrillation. Also, randomized trials comparing warfarin with aspirin have consistently shown a smaller magnitude of stroke reduction than seen in trials comparing warfarin with control or placebo. It seems overwhelmingly likely that aspirin provides some protection against stroke in atrial fibrillation, but the efficacy is clearly much less than that provided by adjusted-dose warfarin.